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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,172	09/29/2003	Stephen Donovan	17510DIV2 (BOT)	5916

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,172	DONOVAN, STEPHEN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-28,36 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-28, 36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 13, 2006 has been entered. Claim 22 had been amended. Claims 1-21 and 29-35 have been cancelled. Claims 36-37 have been added.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendment and response the following rejections have been withdrawn:

a) rejection of claims 22 and 26-29 pages 2-3, paragraph 3 of Final Office action.

b) rejection of claims 22 and 25-29 pages 4-6, paragraph 4 of Final Office action.

c) rejection of claims 22-29 pages 7-9, paragraph 5 of Final Office action.

d) rejection of claims 22 and 26-30 pages 10-12, paragraph 6 of Final Office action.

New Grounds of Rejection

Claim Objection

4. Claim 37 is objected to for the following informality: a sentence should end in a period (.). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 25 recites the phrase "less than 10 Mhz". It is not clear as to what Applicant intends since less than 10 Mhz includes zero. Correction and/or clarification is required.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 22-23, 26-28 and 36 rejected under 35 U.S.C. 102(e) as being anticipated by Graham (*U.S. Patent No. 6,939,852 B2 published September 6, 2005).*

The applied reference has a common Assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art

under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 22-23, 26 –28 and 36 drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of: (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum and (b) applying a fluid to the patient's skin, (c) applying a transdermal patch containing botulinum toxin provided in a dry state to the skin of the patient in an are that had had the stratum corenum disrupted in step (a) and (d) solubilizing the botulinum toxin provided in the dry state with the fluid.

Graham teaches a method of reducing neurotransmitter release in a subdermal structure of a patient by applying a transdermal patch comprising botulinum toxin to the skin (column 1). Graham teach that strong binding of the botulinum toxin to the presynaptic cholinergic nerve ending and the resulting inhibition of exocytosis of acetylcholine by lowering the frequency of acetylcholine release (column 1). Thus, the prior art reference teaches the claim limitation "a method of reducing neurotransmitter release". Graham teach that the transdermal patch of the invention is an adhesive patch for use in conjunction with a skin permeation enhancer (column 4). Graham teach that the application of the botulinum toxin adhesive can be used concurrently or in conjunction with ethanol wipes, dermal abrasion or permeation enhancement such as iontophoresis (column 3). The claim limitations " wherein the stratum corenum is

disrupted by passing an electrical current from a first point to a second point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures" and " are taught in the art because Graham teach that the application of the botulinum toxin adhesive can be used concurrently or in conjunction with ethanol wipes, dermal abrasion or permeation enhancement such as iontophoresis (column 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 25 and 37 are rejected under 35 U.S.C. 103(a) as unpatentable over Graham (*U.S. Patent No. 6,939,852 B2 published September 6, 2005)* as applied to claims 22-23, 26-28 and 36 above and in view of Mitragotri et al *(Science, Vol. 269, August 11, 1995)*.

Claims 25 and 37 are drawn the method of claim 211, wherein the stratum corneum is disrupted by applying ultrasaound at a frequency between 20 kHz and less than 10 Mhz at an intensity that does not permanently damage the patient's skin and

the method of claim 25 wherein the ultrasound application is delivered prior to application of botulinum toxin to the skin.

Graham teaches a method of reducing neurotransmitter release in a subdermal structure of a patient by applying a transdermal patch comprising botulinum toxin to the skin (column 1). Graham teach that strong binding of the botulinum toxin to the presynaptic cholinergic nerve ending and the resulting inhibition of exocytosis of acetylcholine by lowering the frequency of acetylcholine release (column 1). Thus, the prior art reference teaches the claim limitation "a method of reducing neurotransmitter release". Graham teach that the transdermal patch of the invention is an adhesive patch for use in conjunction with a skin permeation enhancer (column 4). Graham teach that the application of the botulinum toxin adhesive can be used concurrently or in conjunction with ethanol wipes, dermal abrasion or permeation enhancement such as iontophoresis (column 3). The claim limitations " wherein the stratum corenum is disrupted by passing an electrical current from a first point to a second point on the patient's skin to a second point on the patient's skin" and "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures" and " are taught in the art because Graham teach that the application of the botulinum toxin adhesive can be used concurrently or in conjunction with ethanol wipes, dermal abrasion or permeation enhancement such as iontophoresis (column 3).

Graham does not specifically teach the use of ultrasound.

Mitragotri et al teach a method of applying ultrasound to promote deliver therapeutic doses of proteins across the skin of a patient (see the Abstract). Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 KHz (see the Abstract). Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins (page 850).

Therefore, it would be *prima facie* obvious at the time the invention was made to modify the method of Graham et al include using ultrasound to enhance the penetration of high molecular weight protein across a patient's skin (e.g. physically disrupt the stratum corneum), apply a fluid to the patient's skin (contained in the transdermal patch) and apply a transdermal patch to the patient's skin to deliver botulinum toxin to skin of a patient because Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins and Graham teaches a method of reducing neurotransmitter release in a subdermal structure of a patient by applying botulinum toxin to the skin of a patient to influence acetylcholine release. It would be expected barring evidence to the contrary that a method of reducing neurotransmitter release can be achieved by using ultrasound to physically disrupt the stratum corenum, applying a chemical enhance to further disrupt the stratum corenum and applying botulinum toxin to the disrupt the stratum corenum in the form of a transdermal patch.

8. Claims 22-28 and 36-37 are rejected under 35 U.S.C. 103(a) as unpatentable over Schmidt *(DE 198 52 981 A1 published May 18, 2000)* in view of Mitragotri et al *(Science, Vol. 269, August 11, 1995)* and Glenn et al (*U.S. Patent No. 6,797,276 published September 28, 2004).*

Claims 22-28 and 36-37 drawn to a method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of: (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum and (b) applying a fluid to the patient's skin, (c) applying a transdermal patch containing botulinum toxin provided in a dry state to the skin of the patient in an are that had had the stratum corenum disrupted in step (a) and (d) solubilizing the botulinum toxin provided in the dry state with the fluid.

Schmidt teaches a method of reducing neurotransmitter release in a subdermal structure of a patient by applying botulinum toxin to the skin of a patient to influence acetylcholine dependent bodily functions (page 1). Schmidt et al teach that strong and irreversible binding of the botulinum toxin to the presynaptic cholinergic nerve ending and the resulting inhibition of exocytosis of acetylcholine by lowering the frequency of acetylcholine release (page 4). Thus, the prior art reference teaches the claim limitation "a method of reducing neurotransmitter release".

Schmidt et al do not teach applying a transdermal patch containing botulinum toxin provided in a dry state to the skin of a patient in an area that had had the stratum corenum disrupted and solubilizing the botulinum toxin provided in the dry state with the

fluid or non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneun and Schmidt et al do not teach the use if ultrasound.

Glenn et al teach a method of transcutaneous immunization system where topical application of an antigen to intact skin (see the Abstract). Glenn et al teach that immune response can be enhanced by physical or chemical penetration (see the Abstract). Glenn et al teach a patch that is used to apply an antigen to the skin (column 5, lines 38-51). Glenn et al teach that antigens from Clostridium botulinum can be used as the antigen used in the invention (column 7). Glenn et al teach that the patch contain penetration enhancers or a device for physical penetration enhancement (column 5, lines 38-51). Glenn et al teach that the disruption of the stratum corneum include tape striping or abrasives which remove the outer laver of the skin (column 8, lines 32-67).

Mitragotri et al teach a method of applying ultrasound to promote deliver therapeutic doses of proteins across the skin of a patient (see the Abstract). Mitragotri et al teach that the ultrasound is used at a low frequency of about 20 KHz (see the Abstract). Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins (page 850). The prior art teaches the claim limitations "wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin and removing the adhesive material applied thereto because Glenn et al teach that tape stripping is a physical enhancer used in their invention (column 8, lines 32-67). The claim limitations " wherein the stratum corneum is disrupted by passing an electrical current from a first point to a second point on the patient's skin to a second

point on the patient's skin", "wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures" and "wherein the ultrasound application is delivered prior to the application of the botulinum toxin to the skin" are taught in the art because Mitragotri et al teach that ultrasound can promote transdermal delivery Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins.

Therefore, it would be *prima facie* obvious at the time the invention was made to modify the method of reducing neurotransmitter release of Schmidt et al to include applying a transdermal patch as taught by Glenn et al and include the use of ultrasound as taught by Mitragotri et al to enhance the penetration of high molecular weight protein across a patient's skin (e.g. physically disrupt the stratum corneum) because Mitragotri et al teach that ultrasound can promote transdermal delivery of high molecular weight proteins and Glenn et al teach a patch that is used to apply an antigen to the skin in a transdermal patch and other chemical enhancers are used in the transdermal patch. It would be expected barring evidence to the contrary that a method of reducing neurotransmitter release can be achieved by using ultrasound to physically disrupt the stratum corenum, applying a chemical enhance to further disrupt the stratum corenum and applying botulinum toxin to the disrupt the stratum corenum in the form of a transdermal patch.

Status of Claims

9. No claims allowed.

Conclusion

10. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
January 27, 2007

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER